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(54) **ENTERIC FILM COATING COMPOSITIONS, METHOD OF COATING THEREWITH, AND COATED FORMS**

ENTERISCHE FILMÜBERZÜGE, VERFAHREN ZUR BESCHICHTUNG DAMIT SOWIE ÜBERZOGENE ARZNEIFORMEN

COMPOSITIONS POUR ENROBAGE PELLICULAIRE GASTRO-RESISTANT, PROCEDE D'ENROBAGE UTILISANT CES COMPOSITIONS, ET FORMES PHARMACEUTIQUES AINSI ENROBEES

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Description

[0001] This invention relates to the field of aqueous enteric film coating suspensions for coating pharmaceutical tablets and the like for preventing release of the ingredients of the coated tablet in the gastric juices of the stomach, and for releasing the ingredients of the tablet in the intestines. It provides a non-toxic edible enteric film coating dry powder composition for use in making an aqueous enteric coating suspension that may be used in coating pharmaceuticals with an intestinally soluble coating that is nsoluble in the gastric juices of the stomach.

BACKGROUND OF THE INVENTION

[0002] Enteric coating solutions that require organic solvents have been used in the past. However, because of the problems associated with the use of organic solvents (i.e., pollution of the atmosphere, safety and hygiene problems for workers, danger of fire and explosion, and expensive equipment requirements to limit or reduce the danger of fire or explosion), aqueous enteric film coating suspensions, such as the COATERIC enteric film coating system of Colorcon, West Point, Pennsylvania, were developed. The COATERIC system is disclosed in Colorcon U.S. Patent No. 4,556,552, which issued on December 3, 1985,in the corresponding international application WO85/01207 and in Colorcon U.S. Patent No. 4,704,295 which issued on November 3, 1987.

[0003] Other known aqueous enteric film coating systems include an aqueous dispersion of acrylic resins, for example, polymethacryl methacrylate copolymer, and dispersions of acetates, for example, cellulose acetate phthalate.

[0004] A problem associated with the known aqueous enteric coating suspensions is tackiness of the coating.

[0005] Another problem with the known aqueous enteric coating systems is that they require at least three processing steps to form the enteric coating suspension. For instance, with the EUDRAGIT system, plasticizer, antifoam, and talc are mixed stepwise into the EUDRAGIT dispersion. With the AQUATERIC - celllulose acetate phthalate dispersion system, the AQUATERIC powder is dispersed in water, followed by stepwise addition of plasticizer, and Tween 80 to form the AQUATERIC suspension. With the COATERIC system, the COATERIC powder, an antifoam, and ammonium hydroxide are mixed into water to form the COATERIC suspension. The need for three processing steps is a drawback because the more processing steps there are, the higher the chances of processing error occurring.

[0006] In the Colorcon U.S. Patent Nos. 4,556,552 and 4,704,295, Colorcon's COATERIC non-toxic edible enteric film coating dry powder, which comprises polyvinyl acetate phthalate (PVAP), a water-soluble plasticizer, an auxiliary film-forming suspending polymeric agent for the PVAP, and pigment particles, is mixed into water, and after the enteric dry powder is thoroughly wetted, an ammonium hydroxide solution is added to form an enteric coating suspension. Although the COATERIC coating suspension forms a very good enteric coating, the COATERIC suspension has the smell of ammonium hydroxide.

SUMMARY OF THE INVENTION

[0007] It is an object of the invention to provide an enteric coating that is less tacky than known aqueous-based enteric film coatings.

[0008] Another object of the invention to provide an aqueous enteric coating suspension that only requires two processing steps to form the enteric coating suspension.

[0009] Another object of the invention is to provide an aqueous enteric coating suspension that does not have the odor of ammonium hydroxide.

[0010] Another object of the invention is to provide a pre-plasticized powder blend enteric coating composition.

[0011] These and other objects are accomplished by our invention, which is described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Fig. 1 shows a graph of test results regarding percent drug dissolved (average of 6 dissolutions) versus time (minutes), for aspirin cores coated in accordance with Example 1.

DETAILED DESCRIPTION OF THE INVENTION

[0013] A non-toxic edible enteric film coating dry powder composition for use in making an aqueous enteric coating suspension which may be used in coating pharmaceutical tablets and the like comprises an enteric film forming polymer, a detackifier, a viscosity modifier, and an alkalizing/anti-coagulating agent. In a particularly preferred embodiment, the inventive non-toxic edible enteric film coating dry powder composition also includes a solid plasticizer.

[0014] Advantageously, the inventive dry powder compositions may include a lubricant, an anti-caking agent, a liquid plasticizer, and a pigment.

[0015] A method of making the inventive non-toxic edible film coating dry powder composition comprises the steps of mixing an enteric film forming polymer with a detackifier, a viscosity modifier, and an anti-coagulating/alkalizing agent, and optionally with one or more of the following components, until a dry homogeneous powder mixture is produced: a solid plasticizer, a lubricant, an anti-caking agent, a liquid plasticizer, and a pigment. The resulting enteric film coating dry powder composition is readily dispersible in deionized water to form a liquid enteric coating suspension and is ready to use in 30 to 45 minutes.

[0016] The invention also includes an aqueous enteric coating suspension for making an enteric coating for pharmaceutical tablets and the like which comprises an enteric film forming polymer, a detackifier, a viscosity modifier, an alkalizing agent, a plasticizer, and an antifoaming agent mixed into water. Advantageously, the inventive suspension may include an optional lubricant, an optional anti-caking agent, and/or an optional pigment.

[0017] A method of making the aqueous enteric coating suspension of the invention comprises mixing the antifoaming agent into water, mixing the inventive enteric dry powder composition, or the individual ingredients of the inventive enteric dry powder composition separately, into the water, and stirring until a homogeneous suspension is produced. When using an embodiment of the inventive enteric dry powder composition that does not have a plasticizer mixed into it, a plasticizer, preferably a liquid plasticizer, is mixed into the water, preferably after the step of mixing the anti-foam into the water.

[0018] The inventive suspension may include a solid plasticizer in combination with a liquid plasticizer. In such a suspension, the liquid plasticizer may be mixed into the enteric dry powder coating composition to become part of the enteric dry powder coating composition of the invention, or the liquid plasticizer may be added separately to the water when preparing the inventive suspension.

[0019] The invention also includes a method of coating substrates such as pharmaceutical dosage forms like tablets and the like with a non-toxic edible enteric film coating, which comprises the steps of forming the inventive aqueous enteric coating suspension as discussed above, applying the inventive aqueous coating suspension onto the substrates to form a film coating on the substrates, and drying the film coating on said substrates.

[0020] The enteric film forming polymer is PVAP-T (titanized polyvinyl acetate phthalate), PVAP-J (polyvinyl acetate phthalate which has been jet milled), HPMCP (hydroxypropyl methylcellulose phthalate), HPMCAS (hydroxypropyl methylcellulose acetate succinate), or CAP (cellulose acetate phthalate). The titanized polyvinyl acetate phthalate (PVAP-T), comprises about 10% titanium dioxide mixed into polyvinyl acetate phthalate (PVAP), while it is being made. A preferred enteric polymer is PVAP-T.

[0021] Preferably, the enteric polymer has a particle size such that 90% of the polymer particles are under 25 microns, and more preferably, under 13 microns.

[0022] The enteric polymer is about 65-85% by weight of the dry powder composition, and is preferably in the range of about 65-81% by weight of the dry powder composition.

[0023] The detackifier is talc, aluminum hydrate, or mixtures thereof. The detackifier is about 5-15% by weight of the dry powder composition, and is preferably in the range of about 6-12% by weight of the dry powder composition.

[0024] The viscosity modifier is sodium alginate, hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC), sodium carboxymethycellulose (sodium CMC), polyvinylpyrrolidone (PVP), Konjac flour, carrageenan, xanthan gum, other hydrophilic polymers, or mixtures thereof. The viscosity modifier is present in the dry powder composition to assist in the forming of a film on the tablets and to act as a suspending agent for the insoluble components in the coating suspension, as well as adding viscosity to the coating suspension. The viscosity modifier helps the coating to adhere to the tablet surface while the enteric polymer particles are fusing to form a film. In other words, the viscosity modifier makes the coating suspension thicker and thereby inhibits settlement and acts as a suspending agent, and also acts as a film former. A preferred viscosity modifier is a medium viscosity grade of sodium alginate (e.g., Kelco Manugel A3B812 sodium alginate).

[0025] The viscosity modifier is about 0.5 to 7% by weight of the dry powder composition, and is preferably in the range of about 1-6% by weight of the dry powder composition.

[0026] The alkalizing agent is a bicarbonate, a carbonate, a phosphate, or a hydroxide of sodium or potassium, magnesium carbonate, magnesium hydroxide, ammonium carbonate, ammonium bicarbonate, magnesium oxide, calcium hydroxide, or mixtures thereof.

[0027] The alkalizing agent is about 1-15% by weight of the dry powder composition, and is preferably in the range of about 1.5-12% by weight of the dry powder composition. Sodium bicarbonate and/or sodium carbonate as the alkalizing agent are preferably used in a range of about 2.0% to about 6% by weight of the dry power composition, and more preferably used in a range of about 2.0% to about 4.5% since above 6% may lead to tackiness problems. When using tri-sodium phosphate as the alkalizing agent, a range of 4.5% to 7% by weight of the dry power composition is preferred for tri-sodium phosphate (anhydrous) and a range of 8% to 12% by weight of the dry power composition is preferred for tri-sodium phosphate (hydrated).

[0028] The alkalizing agent acts as an anti-coalescing or stabilizing agent to raise the agglomeration or gel temperature of the coating suspension to prevent coalescing or blockage of the spray lines and guns. The alkalizing agent also reduces the tackiness of the coating.

[0029] The solid plasticizer is polyethylene glycol having a molecular weight of 1500 to 8000, or Pluronic F86 (a block co-polymer of ethylene oxide and propylene oxide (EO/PO)), or mixtures thereof. The preferred solid plasticizer is polyethylene glycol 3350 (PEG 3350) or polyethylene glycol 4000 (PEG 4000).

[0030] The solid plasticizer when included in the inventive enteric dry powder composition is about 1-20% by weight of the dry coating composition, and is preferably about 1-18% by weight of the dry coating composition.

[0031] The liquid plasticizer may be triethylcitrate, glyceryl triacetate, acetyltriethylcitrate, dibutyl sebacate, diethyl phthalate, polyethylene glycol 400, glycerol, castor oil, or mixtures thereof.

[0032] When the liquid plasticizer is included in the dry powder composition of the invention, the liquid plasticizer is in a range of greater than 0% to about 6% by weight of the dry powder composition. The dry powder composition of the invention is still dry even though it may contain about 4% - 6% liquid plasticizer by weight of the dry powder composition.

[0033] When no plasticizer is included in the dry powder coating composition of the invention or when no liquid plasticizer is included in the dry powder coating composition of the invention, about 5% to about 20% of liquid plasticizer by weight of the dry solid ingredients of the coating suspension of the invention is mixed separately into the coating suspension of the invention.

[0034] The inventive coating suspension has about 5% to about 20% of solid plasticizer, liquid plasticizer, or a combination of solid plasticizer and liquid plasticizer by weight of the non-water ingredients of the inventive coating suspension.

[0035] The lubricant is stearic acid, which is in a range from 0% to about 3% by weight of the dry coating composition.

[0036] The anti-caking agent may be Cabosil, fumed silica made by Cabot, Inc., which is present in a range from 0% to about 2% by weight of the dry powder composition, and preferably is present in a range from 0% to 1.5% by weight of the dry powder coating composition. The anti-caking agent acts as a processing aid and also keeps the dry powder from lumping up while in storage. Use of this anti-caking agent is optional because any lumps that are formed are screened out as part of the preparation of the dispersion.

[0037] The pigment may be any of the pigments used in making coating dispersions for pharmaceutical tablets and the like. For example, the pigments may be FD&C and D&C lakes, titanium dioxide, magnesium carbonate, talc, pyrogenic silica, iron oxides, channel black, and insoluble dyes. Also, natural pigments such as riboflavin, carmine 40, curcumin, and annatto. Other examples of suitable pigments are listed in Jeffries U.S. Patent No. 3,149,040; Butler et al. U.S. Patent No.3,297,535; and Colorcon U.S. Patent No. 3,981,984.

[0038] The pigment may also include lake blends, which contain a plasticizer, and OPADRY pigmented coating compositions, some of which are disclosed in Colorcon U.S. Patent No. 4,543,370 issued on September 24, 1985.

[0039] The pigment, in addition to adding color to the coating of the invention, also acts as an anti-gelling agent.

[0040] The pigment is in a range from 0% to about 25% by weight of the dry coating composition, and preferably is in a range from 0% to about 15% by weight of the dry powder composition.

[0041] The antifoaming agent is a silicone based antifoam, such as Antifoam FG-10 made by Dow Corning. The antifoaming agent is in a range from about 0.1% to about 5% by weight of the dry powder composition, and is preferably about 0.5% to about 5% by weight of the dry powder composition.

[0042] The inventive dry powder non-toxic enteric coating composition is to be made and sold by Colorcon, West Point, Pennsylvania 19486, under the trademark SURETERIC.

[0043] The following examples further illustrate the invention.

EXAMPLE 1

[0044] 12 kilograms of aspirin cores (325mg of aspirin per tablet) are to be coated with a clear subcoat made from a clear OPADRY coating dispersion, an enteric coating of the invention over the subcoat, and a pigmented topcoat over the enteric coating, the topcoat being made from an OPADRY II coating dispersion.

[0045] The clear OPADRY subcoat dispersion of this Example 1 is made by mixing 120 grams of clear OPADRY coating composition (formula YS-2-7013) into 1480.0 grams of deionized water using a propeller mixer for 45-60 minutes to obtain the subcoat suspension. The subcoat suspension has 7.5% w/w total solids. The OPADRY coating composition is manufactured by Colorcon, West Point, Pennsylvania.

[0046] The inventive SURETERIC enteric dry powder composition of this Example 1 is prepared by throughly mixing 24.00 grams of the liquid plasticizer, Citroflex triethylcitrate, into 876.00 grams of PVAP-T in a V-blender. Then, 113.52 grams of talc, 40.80 grams of sodium bicarbonate, 96.00 grams of PEG 3350, 21.60 grams of stearic acid, 16.80 grams of sodium alginate, and 11.28 grams of Cabosil EH5 silica is added to the mixture of PVAP-T and liquid plasticizer and mixed into it for about 10 minutes. The mixture then is passed through a grinder, and then mixed again for 10 more

minutes.

[0047] The inventive enteric suspension of the invention is prepared by mixing 1200.0 grams of the inventive enteric dry powder composition into 6800.0 grams of deionized water in a blender for about 1 hour. Before adding the enteric dry powder composition to the water, 12 grams of a 10% Antifoam FG-10 solution is mixed into the 6800.0 grams of distilled water. The total solids in the enteric suspension is 15.0% w/w.

[0048] The pigmented OPADRY II topcoat suspension is prepared by mixing 360.0 grams of pigmented OPADRY II coating composition (formula Y-22-13570) into 1440.0 grams of distilled water using a propeller mixer for 45-60 minutes. The total solids in the topcoat suspension is 20% w/w. The pigmented OPADRY II coating composition is made by Colorcon, West Point, Pennsylvania.

[0049] The enteric suspension is passed through a 60 mesh screen prior to commencement of spraying.

[0050] The 12 kilograms of aspirin cores (352 mg of aspirin per tablet) are placed in a 24 inch Accela-Cota pan, which has 4 mixing baffles, a Cole-Parmer Masterflex pump having 2 pump heads, Silicone 7015 tubing, 2 Binks 605 spray guns, 66SS fluid nozzles, and 66SH air caps, for coating. The tablets are first given a subcoat using a clear OPADRY subcoat suspension, followed by an enteric coating with the enteric suspension of this Example 1, which is followed by a topcoat of the pigmented OPADRY II topcoat suspension. The spraying conditions are as follows:

	SUBCOAT	ENTERIC COAT	TOP COAT
TABLET LOAD (kg)	12	12	12
FLUID RATE (g/min)	60	70	60
ATOMIZING AIR (psi)	35	35	35
AIR TEMPERATURE (°C)			
INLET	70	69	67
EXHAUST	43	41	43
PAN SPEED (rpm)	15	15	15
COATING TIME (min)	27	114	30
POST DRYING	none	none	none
% WEIGHT GAIN	1	10	3

[0051] The final coated tablets were evaluated using a modified U.S.P. disintegration method. 50 tablets were stressed for 100 revolutions in a fibrilator. Then, the 50 stressed tablets were placed in a basket assembly and immersed for 1 hour in simulated gastric fluid. The basket was moved up and down in the simulated gastric fluid at a rate of about 28-32 strokes/min.

[0052] 50 unstressed tablets were also placed in a basket assembly and immersed for 1 hour in simulated gastric fluid. The basket was moved up and down in the simulated gastric fluid at a rate of about 28-32 strokes/min.

[0053] The integrity of the tablets was evaluated after removal from the simulated gastric fluid. None of the tablets exhibited signs of bloating, cracks, or fissures.

[0054] The results of the tests are as follows:

UNSTRESSED: 0% FAILURE
STRESSED: 0% FAILURE

[0055] A dissolution test was also made on the coated tablets of this Example 1. Using U.S.P. apparatus I (baskets), 6 tablets coated as described in this Example 1 were placed in 0.1N HCL for 2 hours. The release in the acid phase of the test after 2 hours was 0.31%, as compared with the upper limit of not more than 10%. The 6 tablets were then placed in 6.8 phosphate buffer, and the amount of aspirin released in the buffer phase of the test was greater than 85% in thirty minutes, as compared with the official compendial requirement of not less than 80% in 90 minutes. These test results are illustrated in the graph shown in Fig. 1.

EXAMPLE 2

[0056] 12 kilograms of Diclofenac sodium cores (75mg Diclofenac sodium per tablet) are to be coated with a clear subcoat made from a clear OPADRY coating dispersion, an enteric coating of the invention over the subcoat, and a clear topcoat over the enteric coating, the topcoat also being made from an OPADRY coating dispersion. Diclofenac sodium cores are alkaline substrates, and it is very difficult to coat alkaline substrates with an enteric coating.

[0057] The clear OPADRY subcoat dispersion and the clear OPADRY topcoat dispersion of this Example 2 are each

made by mixing 120 grams of clear OPADRY coating composition (formula YS-2-7013) into 1480.0 grams of deionized water using a propeller mixer for 45-60 minutes to obtain the sub coat and topcoat suspensions. The subcoat suspension and the topcoat suspension each have 7.5% w/w total solids. The OPADRY coating composition is manufactured by Colorcon, West Point, Pennsylvania.

[0058] The inventive SURETERIC enteric dry powder composition of this Example 2 is prepared by throughly mixing 24.00 grams of the liquid plasticizer, Citroflex triethylcitrate, into 876.00 grams of PVAP-T in a V-blender. Then, 113.52 grams of talc, 40.80 grams of sodium bicarbonate, 96.00 grams of PEG 3350, 21.60 grams of stearic acid, 16.80 grams of sodium alginate, and 11.28 grams of Cabosil EH5 silica are added to the mixture of PVAP-T and liquid plasticizer and mixed into the mixture for about 10 minutes. The mixture then is passed through a grinder, and then mixed again for 10 more minutes.

[0059] The inventive enteric suspension of the invention is prepared by mixing 1200.0 grams of the inventive enteric dry powder composition into 6800.0 grams of deionized water in a blender for about 1 hour. Before adding the enteric dry powder composition to the water, 12 grams of a 10% Antifoam FG-10 solution is mixed into the 6800.0 grams of distilled water. The total solids in the enteric suspension is 15.0% w/w.

[0060] The enteric suspension is passed through a 60 mesh screen prior to commencement of spraying.

[0061] The 12 kilograms of Diclofenac sodium cores (75 mg Diclofenac sodium per tablet) are placed in a 24 inch Accela-Cota pan, which has 4 mixing baffles, a Cole-Farmer Masterflex pump having 2 pump heads, Silicone 7015 tubing, 2 Binks 605 spray guns, 66SS fluid nozzles, and 66SH air caps, for coating. The tablets are first given a subcoat using the clear OPADRY subcoat suspension, followed by an enteric coating with an enteric suspension of this Example 2, which is followed by a topcoat of the OPADRY suspension. The spraying conditions are as follows:

	SUBCOAT	ENTERIC COAT	TOP COAT
TABLET LOAD (kg)	12	12	12
FLUID RATE (g/min)	60	70	60
ATOMIZING AIR (psi)	35	35	35
AIR TEMPERATURE (°C)			
INLET	74	72	72
EXHAUST	43	41	43
PAN SPEED (rpm)	15	15	15
COATING TIME (min)	27	114	27
POST DRYING	none	none	none
% WEIGHT GAIN	1	10	3

[0062] The final coated tablets were evaluated using a modified U.S.P. disintegration method. 50 tablets were stressed for 100 revolutions in a fribilator. Then, the 50 stressed tablets were placed in a basket assembly and immersed for 1 hour in simulated gastric fluid. The basket was moved up and down in the simulated gastric fluid at a rate of about 28-32 strokes/min.

[0063] 50 unstressed tablets were also placed in a basket assembly and immersed for 1 hour in simulated gastric fluid. The basket was moved up and down in the simulated gastric fluid at a rate of about 28-32 strokes/min.

[0064] The integrity of the tablets was evaluated after removal from the simulated gastric fluid. None of the tablets exhibited signs of bloating, cracks, or fissures.

[0065] The results of the tests are as follows:

UNSTRESSED: 0% FAILURE
STRESSED: 0% FAILURE

[0066] Six of the 50 stressed tablets from the simulated gastric fluid dissolution test and six of the 50 unstressed tablets from the simulated gastric dissolution test were placed in a basket assembly and immersed for one hour in simulated intestinal fluid. The basket was moved up and down in the simulated intestinal fluid at a rate of about 28-32 strokes per minute. The six stressed tablets and the six unstressed tablets all disintegrated within 8 minutes.

[0067] Examples 3-93 further illustrate the invention, all percentages being by weight. In examples 3, 5-9, 11-21, 24, 27, 28, 33-44, 52, 61, and 62, the components of each formulation are mixed together, formed into an enteric coating suspension, and applied to tablets, as in Examples 1 and 2.

[0068] In Examples 4, 10, 23, 29-32, 45-51, 53-60, and 80-93, the components of the formulations are dry mixed together to form the enteric dry powder composition, and then the enteric dry powder composition is formed into an

enteric coating suspension and applied to tables as in Examples 1 and 2.

[0069] In Examples 22, 25, 26, and 63-79, the dry components are mixed together to form the enteric dry powder composition, which is added to water containing antifoam and the liquid plasticizer of the example.

SURETERIC FORMULATIONS										
Raw Material	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
PVAP - T	65.00	81.00	76.00	68.00	73.00	73.00	73.00	67.00	76.00	73.00
Talc 400	12.00	7.00	6.00	12.00	9.50	9.00	8.50	8.00	9.00	8.40
Stearic Acid	2.60	0.00	2.60	2.60	1.80	1.80	1.80	1.50	0.00	2.60
Sodium Alginate	1.80	1.30	1.40	1.80	1.00	2.00	1.40	1.40	1.50	1.40
PEG 3350	12.00	6.90	8.40	9.40	8.30	8.00	6.00	18.00	8.00	8.00
Citroflex - 2	2.40	0.00	2.20	2.20	2.00	2.00	4.00	0.00	2.00	2.00
Sodium bicarbonate	3.00	3.60	3.40	3.20	3.40	3.40	3.40	3.20	3.40	3.40
Cabosil EH5	1.20	0.20	1.00	1.00	1.00	1.00	0.90	0.90	1.10	1.00
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

SURETERIC FORMULATIONS										
Raw Material	#13	#14	#15	#16						
PVAP - T	78.00	74.00	73.00	73.00						
Talc 400	9.00	9.00	8.90	8.50						
Stearic Acid	1.80	2.00	1.80	1.30						
Sodium Alginate	1.40	1.50	1.40	1.40						
PEG 3350	7.80	8.00	8.00	8.00						
Citroflex - 2	2.20	2.00	2.00	2.00						
Sodium bicarbonate		3.40	3.40	3.40						
Sodium Hydroxide	2.00									
Cabosil EH 5	1.00	0.00	1.50	2.00						
Total	100.00	100.00	100.00	100.00						

SURETERIC FORMULATIONS										
Raw Material	#22	#23	#24	#25	#26	#27	#28			
PVAP - J	78.50	65.00	65.00	71.00	81.00	68.00	73.00			
Talc 400	8.00	8.00	9.00	9.00	11.00	8.50	10.50			
Stearic Acid		1.50	1.80	1.80	1.80	1.30	1.70			
Sodium Alginate	1.50	1.40	1.50	1.40	1.60					
HPMC E - 50						7.00				
HEC (Natrosol 250 HR)							0.50			
PEG 3350		20.00	16.00	12.50		8.00	8.00			
Citroflex - 2	*11.95	0.00	0.50	*5.00	*20.00	2.00	2.00			
Tri Sodium Phosphate	12.00									
Sodium bicarbonate		3.20	3.20	3.40	3.60	3.40	3.40			
Cabosil EH 5		0.90	1.00	0.90	0.90	1.00	0.90			
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00			
* Citroflex - 2 (Triacetin) will be added to the dispersion externally										

SURETERIC FORMULATIONS							
Raw Materials	$\#_{29}$	$\#_{30}$	$\#_{31}$	$\#_{32}$	$\#_{33}$	$\#_{34}$	$\#_{35}$
PVAP-T	68.00	69.00	69.00	73.50	74.10	73.00	73.00
Talc 400	—	—	8.88	9.14	10.00	9.46	9.46

(continued)

SURETERIC FORMULATIONS							
Raw Materials	#29	#30	#31	#32	#33	#34	#35
Aluminium Hydmte	10.30	8.65	—	—	—	—	—
Stearic Acid	2.80	1.90	1.76	L72	1.80	1.80	1.80
Sodium Alginate	1.40	1.40	1.33	1.42	1.44	1.40	L40
PEG 3350	10.36	9.28	6.65	9.30	7.20	—	—
Pluronic F68	—	—	3.00	—	—	—	—
PEG 4000	—	—	—	—	—	—	8.00
PEG 8000	—	—	—	—	—	8.00	—
Citruflex - 2	—	—	—	—	2.00	2.00	2.00
Bodium Bicarbonate	—	—	—	—	—	3.40	3.40
Sodium Carbonate	—	—	—	4.00	2.50	- -	- -
TSP $12H_2O$	6.10	8.80	8.49	—	—	—	—
Cabosil EH 5	0.94	0.97	0.89	0.92	0.96	0.94	0.94
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Raw Material	#17	Pigment Blend		#19	#20	#21
PVAP - J	73.00	Raw Material	#18	—	—	—
Talc 400	9.46	Labe Blend 1368	55.00	9.46	9.46	9.46
Stearic Acid	1.80	TiO_2	20.00	1.80	1.80	1.80
Sodium Alginate	1.40	PEO 3350	10.00	1.40	1.40	1.40
PEG 3350	8.00	Citroflex - 2	10.00	8.00	8.00	8.00
Citroflax - 2	2.00	Tween 80	3.00	2.00	2.00	2.00
Bodium bicarbonate	3.40			3.40	3.40	3.40
Cabosil EH 6	0.94			0.94	0.94	0.94
HPMCP	—			73.00	—	—
HPMCAB	—			—	73.00	—
CAP	—			—	—	73.00
Toatal	100.00		100.00	100.00	100.00	100.00

Raw Matertal	* 18A	* 18B
* 17 Sureterin clear	94.00	87.50
* 18 Pigment Bleed	6.00	12.50

	EX. 36	EX. 37	EX. 38	EX. 39	EX. 40	EX. 41	EX. 42	EX. 43	EX. 44
Components									
	16%solid	16%solid	16%solid	16%solid	16%solid	16%solid	16%solid	16%solid	20%solid
%PVAP-T*	73	73.2	73.2	67.1	73	70.5	73	73	73
%TALC	9.46	9.46	9.46	8.87	9.48	9.1	9.4	9.46	9.46
%Stearic acid	1.8	1.8	1.8	1.65	1.8	1.74	1.8	1.8	1.8
%Sc. Alginate	1.4	1.4	1.4	1.3	1.4	1.35	1.4	1.4	1.4
%Cabosil	0.94	0.94	0.94	0.88	0.94	0.9	0.94	0.94	0.94
%Sc. Stearb.	4	3.6	3.6	3.3	3.6	3.25	3.38	3.4	3.4
%Citroflex	2.3	2.4	2.4	2	2.2	2.1	2.2	2	2
% Mg Oxide					0.4	0.38	0.38	0.2	0.2
%PEG 3350	7.1	7.2	7.2	16.12	7.2	10.7	7.6	7.8	7.8
% FB - 10	1	1	1	1	1	1	1	1	1

Components	Ex. 45	Ex. 46	Ex. 47	Ex. 48	Ex. 49	Ex. 50	Ex. 51	Ex. 52	Ex. 53	Ex. 54	Ex. 55
%PVAP-J				69.03							
%PVAP-T		71.15	69.68		69	69.1	69.072	69.3	69.75	69.3	71.18
%TALC	9.69	9.13					9.66	9.76	9.66	9.76	9.15
% Al. Hydrate			10.1	9.09	9.65	10.3					
%Stearic acid	1.92	1.82	2.76		1.9	2.0	1.77	1.76	1.78	1.76	1.82
%Sa. Alginate	1.44	1.37	1.38	1.39	1.4	1.4	1.33	1.32	1.34	1.32	1.37
%Cabosil	0.96	0.92	0.92	0.91	0.97	0.94	0.89	0.88	0.9	0.88	0.92
%Sa. Phos.	4 (anh)	8.76	8.12	8.3	8.6	8.1	8.49	8.4	8.66	8.4	8.76
%Citrates								4			
% PVP									2	2	
%PEG 3350	7.3	6.66	10.1	11.34	8.68	10.38	8.65	8.69	8.72	8.69	8.66
%Pluronic F68							3				
% FD - 10	1	1	1	1	1	1	1	1	1	1	1

Components	EX. 56	EX.57	EX.58	EX. 59	EX. 60	EX. 61	EX.62
%PVAP-J							
%PVAP-T	68.03	72.6	73.65	74	73.8	73	73.2
%TALC		8.54	7.84	8.1	8.14	8.48	8.48
% Al. Hydrate	8.08						
%Stearic acid		1.76	1.72	1.76	1.72	1.8	1.8
%So. Alginate	1.38	1.4	1.43	1.42	1.42	1.4	1.4
%Cabosil	0.91	0.9	0.88	0.92	0.92	0.94	0.94
%So. Phos.	8.9	6	4.83				
%Citrofiex						2.3	2.4
% Sod. Borate						4	3.6
%PEG 3350	8.34	8.6	8.07	8.3	8.3	7.1	7.2
% Sod. Carb.				2.64	4		
%Pluronic F68	2						
% Mg. Oxide		1.2	1.2	0.97			
% FG - 10	1	1	1	1	1	1	1

Components	EX. 63	EX. 64	EX. 65	EX. 66
%PVAP-J				
%PVAP-T	80.84	80.84	79.1	78.41
%TALC	10.33	10.33	10.15	9.78
% Al. Hydrate				
%Stearic acid	2.08	2.08	2.02	1.96
%Sa. Alginate	1.64	1.64	1.62	1.47
%Cabosil	1.04	1.04	1.01	0.88
%Sa. Pirce.	4.39 (anh)	4.39(anh)	6.2	9.4
%Citrollex	10.9	10.9	10.7	10.32
%PEG 3350				
%Pluronic F68				
% FG - 10	1	1	1	1

Components	Ex. 67	Ex. 68	Ex. 69	Ex. 70	Ex. 71	Ex. 72	Ex. 73	Ex. 74	Ex. 75	Ex. 76	Ex. 77	Ex. 78	Ex. 79
%PVAP-J	78.6			75.42			78.69						
%PVAP-T		78.24	78.23		80	80.11		80.6	80.73	80.64	72.8	73.45	80
%TALC	9.7	9.77	9.77	9.67	0	10.27	10.22	10.27	10.32	10.32	9.91	9.41	0
% Al. Hydrate													
%Stearic acid	1.94	1.96	1.95	1.93		2.05	2.04	2.06	2.07	2.06	1.96	1.86	
%Sp. Alginate	1.46	1.47	1.46	1.45	1.92	1.84	1.83	1.8	1.85	1.84	1.4	1.46	1.92
%Ethanol	0.97	0.97	0.98	0.97		1.05	1.02	1.03	1.04	1.04	0.93	0.85	
%Sp. Phos.	10.33	9.8	9.81	10.86	10.08	8 (anh.)	8.5 (anh)	4.6 (anh)	4.29 (anh)	4.29 (anh)	3.97 (anh)	3.9 (anh)	10.08
%Diuiles			10.29	11.08									10.08
%Triacetin	10.33	10.29			10.8	10.81	11.98	10.67	10.9	10.9	9.85	8.83	
%Pluronic F68													
% FD-10	1	1	1	1	1	1	1	1	1	1	1	1	1

Components	Ex. 80	Ex. 81	Ex. 82	Ex. 83	Ex. 84	Ex. 85	Ex. 86	Ex. 87	Ex. 88	Ex. 89	Ex. 90	Ex. 91	Ex. 92	Ex. 93
%PVA/AT	70.92	72.5	70.13	70.92	67.77	73.29	70.92	69.25	69.69	72.5	70.13	69.25	69.69	69.25
%TALC	10	8	8	7	10	8	10	8	10	8	8	8	10	8
%Stearic acid	0	2	1	0.5	0	0	0	2	2	2	1	1.5	2	0.5
%Sp. Alginate	1.42	1.45	1.4	1.42	1.35	1.47	1.42	1.39	1.37	1.45	1.4	1.39	1.34	1.39
%Colanyl	0	0	0.5	0.35	1	1	0	1	1	0	0.9	0.75	0	0.25
%Sp. Pres.	0.72	0.62	0.85	0.72	0.34	0.01	0.72	0.85	0.49	0.62	0.85	0.85	0.24	0.85
%PEG 3350	0.84	0.13	0.84	0.84	0.84	0.23	0.84	0.74	0.84	0.13	0.84	0.74	0.44	0.74
%Plasacryl P20	0	0	1.5	2.85	3	0	0	0	0	0	1.5	0.75	0	2.25
3-10	1	1	1	1	1	1	1	1	1	1	1	1	1	1

[0070] The percent solids in the enteric coating suspensions of the invention are about 10% to about 30%, and preferably is about 12% to about 20%.

[0071] It is preferred, but not necessary, to provide a subcoat and a topcoat, such as those described in Examples

1 and 2, on a tablet coated in accordance with the invention. Preferably, the subcoat and the topcoat each comprise, typically, 1-10% of the weight of the tablet, depending on the size, weight, and shape of the tablet. Typically, a small tablet requires a larger percentage of subcoat and topcoat by weight of the tablet then does a larger tablet.

[0072] The enteric coating of the invention comprises, typically, greater than 6% of the weight of the tablet, and preferably between 8% to 12% by weight of the tablet in order to get the enteric results, depending on the size, weight, and shape of the tablet. A small tablet requires a larger percentage of coating by weight of the tablet for enteric coating then does a larger tablet.

[0073] Tablets coated with the inventive coating suspension have an intestinally soluble coating that is insoluble in the gastric juices of the stomach.

[0074] Without the step of adding an antifoaming agent in the method of making the enteric coating suspension of the invention, air bubbles tend to be incorporated into the suspension during mixing of the dry ingredients into the water. Air bubbles, if present in the coating suspension during spraying onto tablets substrates may create pin holes in the film coating, which may lead to failure of the enteric film coating. Further, some of the alkalizing agents, such as sodium bicarbonate, are effervescent, and mixing them into the water of the enteric coating suspension may lead to the formation of additional air bubbles in the enteric coating suspension. Also, sodium alginate tends to maintain any foam or bubbles formed in the enteric coating suspension. The antifoaming agent fights against the incorporation of air bubbles in the enteric coating suspension by causing air bubbles in the enteric coating suspension to rupture.

[0075] The enteric coating of the invention provides an improvement of film properties over the film properties of known enteric film coatings based on aqueous enteric coating suspension. For example, the coating of the invention, when compared with known coatings based on aqueous enteric coating suspensions, has better adhesion, is more resilient, is less friable, and has a significantly lower modulous of elasticity. Further, using a preferred embodiment of the inventive enteric dry powder composition which contains a plasticizer, our inventive aqueous enteric coating suspension requires only two processing steps to form the enteric coating suspension of the invention - mixing antifoam with water and then mixing the enteric powder composition into the antifoam/water mixture.

[0076] A comparison of the inventive SURETERIC system with other enteric aqueous systems appears below.

	SURETERIC	**EUDRAGIT**	**AQUATERIC**	**COATERIC**
PREPARATION STEPS	Mix powder & antifoam with water	Mix plasticizer, antifoam, & talc with dispersion	Mix powder, plasticizer & Tween 80 with water	Mix powder, antifoam, & ammonia with water
PREPARATION STEPS	2	3	3	3
PREPARATION TIME	45-60 min.	60 min.	90-110 min.	60 min.
PROCESS PROBLEMS	1. Slight Tack	1. Tack, 2. High % of talc settles rapidly, 3. Prone to gun clogs	1. 60 min. post-drying step	1. Tack, 2. Ammonia unpleasant to work with

Claims

1. A non-toxic edible enteric film coating dry powder composition for use in making an aqueous enteric coating suspension which may be used in coating pharmaceutical tablets, comprising an enteric film forming polymer, a detackifier, a viscosity modifier, and an alkalizing agent, the composition further comprising a liquid plasticizer.

2. A non-toxic edible aqueous enteric coating suspension for use in coating pharmaceutical tablets, comprising an enteric film forming polymer, a detackifier, a viscosity modifier, an alkalizing agent, a liquid plasticizer, an antifoaming agent, and water.

3. A dry powder composition or aqueous suspension of claim 1 or 2, further including a solid plasticizer and/or a lubricant and/or an anti-caking agent and/or a pigment.

4. A dry powder composition or aqueous suspension of any of claims 1 to 3, the enteric film forming polymer being PVAP-T (titanized polyvinyl acetate phthalate), PVAP-J (polyvinyl acetate phthalate which has been jet milled), HPMCP (hydroxypropyl methylcellulose phthalate), HPMCAS (hydroxypropyl methylcellulose acetate succinate),

or CAP (cellulose acetate phthalate).

5. A dry powder composition or aqueous suspension of any of claims 1, 2, 3 or 4, the polymer being in a range of 55% to 85% by weight, especially in a range of 65% to 81% by weight of the composition or of the non-water ingredients of the suspension.

6. A dry powder composition or aqueous_suspension of any of the claims 1 to 5, the detackifier being talc, aluminum hydrate, or mixtures thereof

7. A dry powder composition or aqueous suspension of any of the claims 1 to 6, the detackifier being in a range of 5% to 15% by weight, especially 6% to 12% by weight, of the composition or of the non-water ingredients of the suspension respectively.

8. A dry powder composition or aqueous suspension of any of the claims 1 to 7, the viscosity modifier being sodium alginate, hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC), sodium carboxymethycellulose (sodium CMC), polyvinylpyrrolidone (PVP), Konjac flour, carrageenan, xanthan gum, other hydrophilic polymers, or mixtures thereof

9. A dry powder composition or aqueous suspension of any of the claims 1 to 8, the viscosity modifier being in a range of 0.5% to 7% by weight, especially 1% to 6% by weight, of the composition or of the non-water ingredients of the suspension.

10. A dry powder composition or aqueous suspension of any of the claims 1 to 9, the alkalizing agent being a bicarbonate, a carbonate, a phosphate, or a hydroxide of sodium or potassium, magnesium carbonate, magnesium hydroxide, ammonium carbonate, ammonium bicarbonate, magnesium oxide, calcium hydroxide, or mixtures thereof

11. A dry powder composition or aqueous suspension of any of the claims 1 to 10, the alkalizing agent being in a range of 1% to 15% by weight, especially 1,5% to 12% by weight, of the composition or of the non-water ingredients of the suspension.

12. A dry powder composition or aqueous suspension of any of the claims 3 to 11, the solid plasticizer being polyethylene glycol having a molecular weight of 1500 to 8000, or Pluronic F86.

13. A dry powder composition or aqueous suspension of any of the claims 3 to 12, the solid plasticizer being in a range of 1% to 20% by weight, especially 1% to 18% by weight, of the composition or of the non-water ingredients of the suspension.

14. A dry powder composition or aqueous suspension of any of the claims 3 to 13, the lubricant being stearic acid.

15. A dry powder composition or aqueous suspension of any of the claims 3 to 14, the lubricant being in a range of greater than 0% to 3% by weight of the composition or of the non-water ingredient of the suspension.

16. A dry powder composition or aqueous suspension of any of the claims 3 to 15, the anti-caking agent being silica.

17. A dry powder composition or aqueous suspension of any of the claims 3 to 16, the anti-caking agent being in a range of greater than 0% to 2% by weight, especially to 1,5% by weight, of the composition or of the non-water ingredients of the suspension.

18. A dry powder composition or aqueous suspension of any of the claims 1 to 17, the liquid plasticizer being triethylcitrate, glyceryl triacetate, acetyltriethylcitrate, dibutyl sebacate, diethyl phthalate, polyethylene glycol 400, glycerol, castor oil, or mixtures thereof

19. A dry powder composition or aqueous suspension of any of the claims 1 to 18, the liquid plasticizer being in a range of greater than 0 to 6% by weight of the composition or of the non-water ingredients of the suspension or in a range of 5% to 20% by weight of the dry solid ingredients of the suspension.

20. A dry powder composition or aqueous suspension of any of the claims 3 to 19, the pigment being lake blends with

plasticizer, FD& C and D&C lakes, titanium dioxide, or OPADRY non-clear film coating compositions.

21. A dry powder composition or aqueous suspension of any of the claims 3 to 20, the pigment being in a range from greater than 0% to 25% by weight, especially to 15% by weight, of the composition or of the non-water ingredients of the suspension.

22. An aqueous suspension of any of the claims 2 to 4 or 6 to 21, the polymer being in a range of 55% to 90% by weight of the non-water ingredients of the suspension, especially in a range of 65% to 81% by weight of the non-water ingredients of the suspension.

23. An aqueous suspension of any of the claims 2 to 4 or 6 to 22, the antifoaming agent being a silicone based antifoam.

24. An aqueous suspension of any of the claims 2 to 4 or 6 to 23, the antifoaming agent being in a range of 0.1% to 5% by weight, especially 0,5% to 5% by weight of the non-water ingredients of the suspension.

25. A method of coating substrates such as pharmaceutical tablets and the like with an enteric film coating, comprising forming the aqueous enteric coating suspension of any of claims 2 to 4 or 6 to 24, applying the aqueous enteric coating suspension onto the substrates to form an enteric film coating on the substrates, and drying the enteric film coating on said substrates.

Patentansprüche

1. Trockenpulverzusammensetzung für nichttoxische, eßbare enterische Filmüberzüge, zur Verwendung bei der Herstellung einer wässrigen enterischen Überzugssuspension, die zum Überziehen von pharmazeutischen Tabletten benutzt werden kann. mit einem enterischen filmbildenden Polymer, einem Klebrigkeitshemmer, einem Viskositätsmodifizierer und einem alkalisierenden Mittel. wobei die Zusammensetzung weiterhin einen flüssigen Weichmacher enthält.

2. Nichttoxische, eßbare, wässrige, enterische Überzugssuspension zur Verwendung beim Überziehen von pharmazeutischen Tabletten, mit einem enterischen filmbildenden Polymer, einem Klebrigkeitshemmer, einem Viskositätsmodifizierer, einem alkalisierenden Mittel, einem flüssigen Weichmacher, einem schäumungshemmendem Mittel und Wasser.

3. Trockenpulverzusammensetzung oder wässrige Suspension nach Anspruch 1 oder 2, weiterhin enthaltend einen festen Weichmacher und/oder ein Schmiermittel und/oder ein Antiverblockungsmittel und/oder ein Pigment.

4. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 3, bei dem das enterische filmbildende Polymer PVAP-T (titanisiertes Polyvinylazetat-Phtalat) PVAP-J (strahlgemahlenes Polyvinylazetat-Phthalat). HPMCP (Hydroxypropyl-Methylzellulose-Phthalat), HPMCAS (Hydroxypropyl-Methylzellulose-Azetat-Succinat) oder CAP (Celluloseazetat-Phthalat) ist.

5. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1, 2. 3 oder 4, bei dem das Polymer im Bereich von 55 bis 85 Gew.%, insbesondere im Bereich von 65 bis 81 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

6. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 5, bei dem der Klebrigkeitshemmer Talkum, Aluminiumhydrat oder ein Gemisch daraus ist.

7. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 6, bei dem Klebrigkeitshemmer im Bereich von 5 bis 15 Gew.%, insbesondere 6 bis 12 Gew.% der Zusammensetzung bzw. der nichtwässrigen Bestandteile der Suspension liegt.

8. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 7, bei dem der Viskositätsmodifizierer Natriumalginat, Hydroxypropyl-Methylzellulose (HPMC) Hydroxyethylzellulose (HEC), Natrium-Karboxymethylzellulose (Natrium-CMC) Polyvinylpyrrolidon (PVP), Konjac-Mehl, Carrageenan, Xanthangummi, andere hydrophile Polymere oder ein Gemisch hieraus ist.

9. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 8, bei der der Viskositätsmodifizierer im Bereich von 0,5 bis 7 Gew.%, insbesondere 1 bis 6 Gew.% der Zusammensetzung oder nichtwässrigen Bestandteile der Suspension liegt.

10. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 9, bei der das alkalisierende Mittel ein Bicarbonat, ein Carbonat, ein Phosphat oder ein Hydroxid von Natrium oder Kalium, Magnesiumcarbonat, Magnesiumhydroxid, Ammoniumcarbonat, Ammoniumbicarbonat, Magnesiumoxid, Kalziumhydroxid oder ein Gemisch hieraus ist.

11. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 10, bei der das alkalisierende Mittel im Bereich von 1 bis 15 Gew.%, insbesondere 1.5 bis 12 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

12. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 11, bei der der feste Weichmacher Polyethylenglykol mit einem Molekulargewicht von 1500 bis 8000 oder Pluronic F86 ist.

13. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 12, bei dem der feste Weichmacher im Bereich von 1 bis 20 Gew.%, insbesondere 1 bis 18 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

14. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 13, bei der das Schmiermittel Stearinsäure ist.

15. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 14, bei dem das Schmiermittel im Bereich von mehr als 0 bis 3 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

16. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 15, bei dem das Antiverblockungsmittel Silika ist.

17. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 16, bei dem das Antiverblockungsmittel im Bereich von mehr als 0 bis 2 Gew.%, insbesondere bis 1.5 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

18. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 17, bei der der flüssige Weichmacher Triethylzitrat, Glyzeryltriazetat, Azetyltriethylzitrat, Dibutylsebacat, Diethylphtalat, Polyethylenglycol 400, Glycerol, Kastoröl oder ein Gemisch hieraus ist.

19. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 1 bis 18, bei der der flüssige Weichmacher im Bereich von mehr als 0 bis 6 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension oder im Bereich von 5 bis 20 Gew.% der trockenen Festbestandteile der Suspension liegt.

20. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 19, bei der das Pigment Farblack-Gemische mit Weichmacher, FD & C- und D & C-Farblacke, Titandioxid oder trübe OPADRY Filmüberzugszusammensetzungen sind.

21. Trockenpulverzusammensetzung oder wässrige Suspension nach einem der Ansprüche 3 bis 20, bei der das Pigment im Bereich von mehr als 0 bis 25 Gew.%, insbesondere bis 15 Gew.% der Zusammensetzung oder der nichtwässrigen Bestandteile der Suspension liegt.

22. Wässrige Suspension nach einem der Ansprüche 2 bis 4 oder 6 bis 21, bei der das Polymer im Bereich von 55 bis 90 Gew.% der nichtwässrigen Bestandteile der Suspension, insbesondere im Bereich von 65 bis 81 Gew.% der nichtwässrigen Bestandteile der Suspension liegt.

23. Wässrige Suspension nach einem der Ansprüche 2 bis 4 oder 6 bis 22, bei der das schäumungshemmende Mittel ein Schaumhemmer auf Silikonbasis ist.

24. Wässrige Suspension nach einem der Ansprüche 2 bis 4 oder 6 bis 23, bei der das schäumungshemmende Mittel im Bereich von 0,1 bis 5 Gew.%, insbesondere 0,5 bis 5 Gew.% der nichtwässrigen Bestandteile der Suspension liegt.

25. Verfahren zum Überziehen von Substraten wie etwa pharmazeutischen Tabletten und dergleichen mit einem enterischen Filmüberzug, umfassend: Herstellen der wässrigen, enterischen Überzugssuspension nach einem der Ansprüche 2 bis 4 oder 6 bis 24, Auftragen der wässrigen enterischen Überzugssuspension auf die Substrate, um einen enterischen Filmüberzug auf den Substraten zu bilden, und Trocknen des enterischen Filmüberzugs auf den Substraten.

Revendications

1. Composition en poudre sèche pour enrobage pelliculaire entérique comestible non toxique utile dans la préparation d'une suspension d'enrobage entérique aqueuse qui peut être utilisée dans l'enrobage de comprimés pharmaceutiques, comprenant un polymère formant une pellicule entérique, un agent anti-adhésif, un agent modifiant la viscosité et un agent alcalinisant, la composition comprenant en outre un plastifiant liquide.

2. Suspension d'enrobage entérique aqueuse comestible non toxique utile dans l'enrobage de comprimés pharmaceutiques, comprenant un polymère formant une pellicule entérique, un agent anti-adhésif, un agent modifiant la viscosité, un agent alcalinisant, un plastifiant liquide, un agent anti-mousse et de l'eau.

3. Composition en poudre sèche ou suspension aqueuse selon la revendication 1 ou 2, comprenant de plus un plastifiant solide et/ou un lubrifiant et/ou un agent anti-agglomération et/ou un pigment.

4. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 3, le polymère formant une pellicule entérique étant un PVAP-T (acétate phtalate de polyvinyle titanisé), un PVAP-J (acétate phtalate de polyvinyle qui a été broyé au jet), HPMCP (phtalate d'hydroxypropyl méthylcellulose), HPMCAS (acétate succinate d'hydroxypropyl méthylcellulose), ou CAP (acétate phtalate de cellulose).

5. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1, 2, 3 ou 4, le polymère étant compris dans une gamme de 55% à 85% en poids, en particulier dans une gamme de 65% à 81% en poids de la composition ou des composants autres que l'eau de la suspension.

6. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 5, l'agent anti-adhésif étant le talc, l'aluminium hydraté ou leurs mélanges.

7. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 6, l'agent anti-adhésif étant compris dans une gamme de 5% à 15% en poids, en particulier 6% à 12% en poids, de la composition ou des composants autres que l'eau de la suspension respectivement.

8. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 7, l'agent modifiant la viscosité étant l'alginate de sodium, l'hydroxypropyl méthylcellulose (HPMC), l'hydroxyéthylcellulose (HEC), la carboxyméthyl cellulose sodique (CMC), une polyvinylpyrrolidone (PVP), une farine de Konjac, une carraghénine, une gomme xanthane, d'autres polymères hydrophiles, ou leurs mélanges.

9. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 8, l'agent modifiant la viscosité étant compris dans une gamme de 0,5% à 7% en poids, en particulier 1% à 6% en poids de la composition ou des composants autres que l'eau de la suspension.

10. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 9, l'agent alcalinisant étant un bicarbonate, un carbonate, un phosphate ou un hydroxyde de sodium ou de potassium, le carbonate de magnésium, l'hydroxyde de magnésium, le carbonate d'ammonium, le bicarbonate d'ammonium, l'oxyde de magnésium, l'hydroxyde de calcium ou leurs mélanges.

11. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 10, l'agent alcalinisant étant compris dans une gamme de 1% à 15% en poids, en particulier 1,5% à 12% en poids de la composition ou des composants autres que l'eau de la suspension.

12. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 11, le plastifiant solide étant un polyéthylène glycol ayant un poids moléculaire de 1500 à 8000, ou le Pluronic F86.

13. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 12, le plastifiant solide étant compris dans une gamme de 1% à 20% en poids, en particulier 1% à 18% en poids de la composition ou des composants autres que l'eau de la suspension.

14. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 13, le lubrifiant étant l'acide stéarique.

15. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 14, le lubrifiant étant compris dans une gamme allant de plus de 0% à 3% en poids de la composition ou des composants autres que l'eau de la suspension.

16. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 15, l'agent anti-agglomération étant une silice.

17. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 16, l'agent anti-agglomération étant compris dans une gamme allant de plus de 0% à 2% en poids, en particulier à 1,5% en poids, de la composition ou des composants autres que l'eau de la suspension.

18. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 17, le plastifiant liquide étant le citrate de triéthyle, le triacétate de glycéryle, le citrate d'acétyltriéthyle, le sébacate de dibutyle, le phtalate de diéthyle, le polyéthylène glycol 400, le glycérol, l'huile de ricin ou leurs mélanges.

19. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 1 à 18, le plastifiant liquide étant compris dans une gamme allant de plus de 0% à 6% en poids de la composition ou des composants autres que l'eau de la suspension ou dans une gamme de 5% à 20% en poids des composants solides secs de la suspension.

20. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 19, le pigment étant choisi parmi des mélanges de laques avec un plastifiant, des laques FD&C et D&C, du dioxyde de titane ou des compositions d'enrobage pelliculaires non transparents OPADRY.

21. Composition en poudre sèche ou suspension aqueuse selon l'une quelconque des revendications 3 à 20, le pigment étant compris dans une gamme allant de plus de 0% à 25% en poids, en particulier à 15%, de la composition ou des composants autres que l'eau de la suspension.

22. Suspension aqueuse selon l'une quelconque des revendications 2 à 4 ou 6 à 21, le polymère étant compris dans une gamme de 55% à 90% en poids des composants autres que l'eau de la suspension, en particulier dans une gamme de 65% à 81% en poids des composants autres que l'eau de la suspension.

23. Suspension aqueuse selon l'une quelconque des revendications 2 à 4 ou 6 à 22, l'agent anti-mousse étant un agent anti-mousse à base de silicone.

24. Suspension aqueuse selon l'une quelconque des revendications 2 à 4 ou 6 à 23, l'agent anti-mousse étant compris dans une gamme de 0,1% à 5% en poids, en particulier 0,5% à 5% en poids des composants autres que l'eau de la suspension.

25. Procédé d'enrobage de substrats comme des comprimés pharmaceutiques et similaires avec un enrobage pelliculaire entérique, comprenant la formation de la suspension d'enrobage entérique aqueuse selon l'une quelconque des revendications 2 à 4 ou 6 à 24, l'application de la suspension d'enrobage entérique aqueuse sur les substrats pour former un enrobage pelliculaire entérique sur les substrats, et le séchage de l'enrobage pelliculaire entérique sur lesdits substrats.

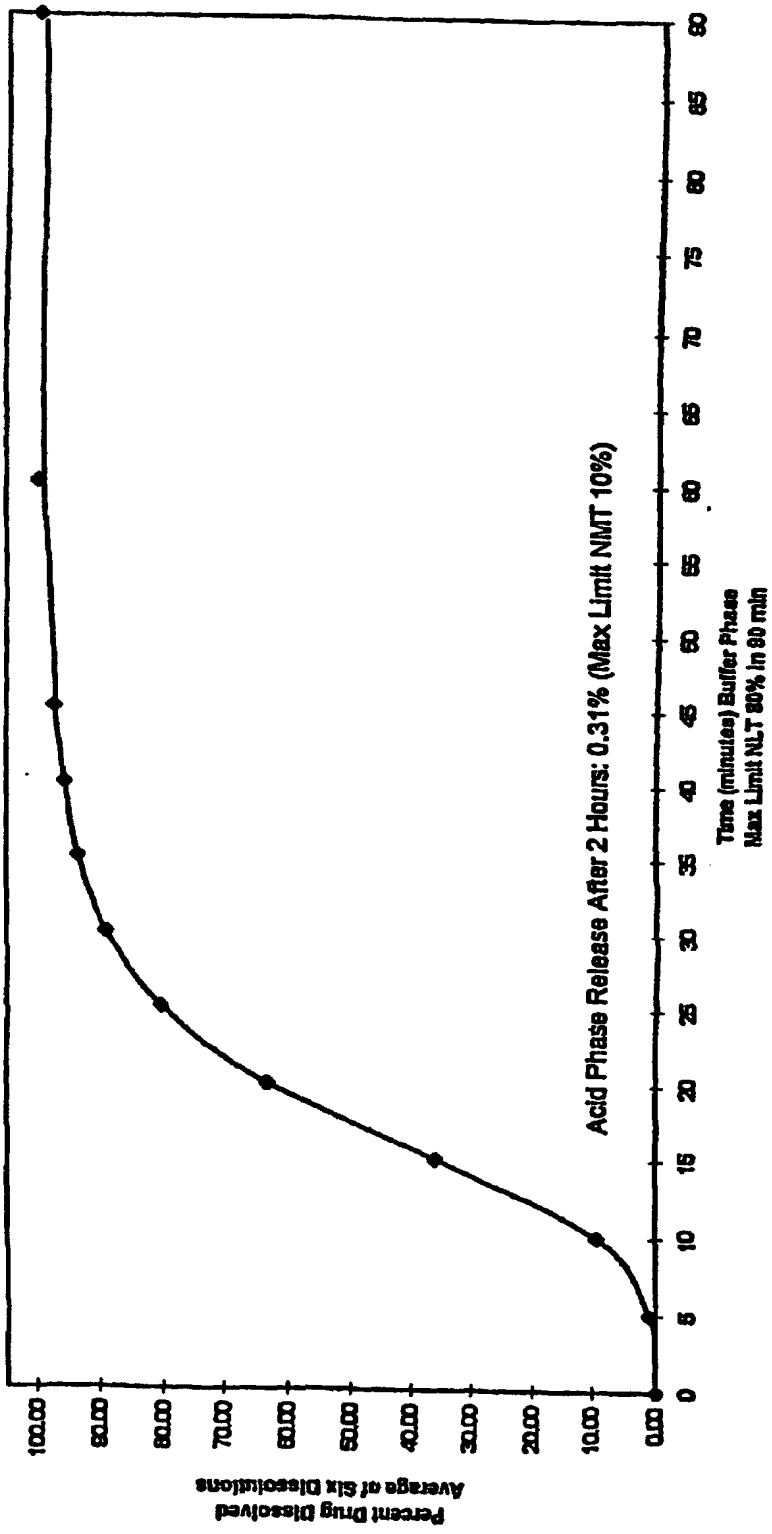
Formula X-08314/Topcoat Y-22-13570
Substrate: 325 mg Aspirin Cores
Dissolution: U.S.P. Method I Delayed Release
Percent Drug Dissolved
Average of Six Dissolutions
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Acid Phase Release After 2 Hours: 0.31% (Max Limit NMT 10%)
Time (minutes) Buffer Phase
Max Limit NLT 80% in 90 min

Figure 1: